



## Original Article

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# The Impact of Diabetes Mellitus on Vascular Biomarkers in Patients with End-Stage Renal Disease

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**Purpose:** Diabetes mellitus (DM) is the most common cause of end-stage renal disease (ESRD) and an important risk factor for cardiovascular (CV) disease. We investigated the impact of DM on subclinical CV damage by comprehensive screening protocol in ESRD patients.

**Materials and Methods:** Echocardiography, coronary computed tomography angiogram, 24-h ambulatory blood pressure monitoring, and central blood pressure with pulse wave velocity (PWV) were performed in 91 ESRD patients from the Cardiovascular and Metabolic disease Etiology Research Center-High risk cohort.

**Results:** The DM group (n=38) had higher systolic blood pressure than the non-DM group (n=53), however, other clinical CV risk factors were not different between two groups. Central aortic systolic pressure (148.7±29.8 mm Hg vs. 133.7±27.0 mm Hg,  $p=0.014$ ), PWV (12.1±2.7 m/s vs. 9.4±2.1 m/s,  $p<0.001$ ), and early mitral inflow to early mitral annulus velocity (16.7±6.4 vs. 13.7±5.9,  $p=0.026$ ) were higher in the DM group. Although the prevalence of coronary artery disease (CAD) was not different between the DM and the non-DM group (95% vs. 84.4%,  $p=0.471$ ), the severity of CAD was higher in the DM group ( $p=0.01$ ). In multivariate regression analysis, DM was an independent determinant for central systolic pressure ( $p=0.011$ ), PWV ( $p<0.001$ ) and the prevalence of CAD ( $p=0.046$ ).

**Conclusion:** Diabetic ESRD patients have higher central systolic pressure and more advanced arteriosclerosis than the non-DM control group. These findings suggest that screening for subclinical CV damage may be helpful for diabetic ESRD patients.

**Key Words:** End-stage renal disease, diabetes mellitus, target organ damage, coronary artery disease, hypertension

## INTRODUCTION

End-stage renal disease (ESRD) patients often suffer from var-

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ious cardiovascular (CV) diseases, which account for considerable morbidity and mortality.<sup>1,2</sup> In addition, diabetes mellitus (DM), which comprises the most common cause of ESRD,<sup>3</sup> is a major risk factor for CV diseases. Thus, it can be reasonably hypothesized that DM would play an additive role in the generation and advancement of CV diseases in ESRD patients compared to patients with ESRD due to other etiologies (non-DM ESRD). With recent advances in diagnostic modalities for CV diseases and our enhanced knowledge of the CV system, we currently have better screening protocols for CV system even in subclinical stage patients. However, comprehensive investigation of the prevalence and features of CV system in ESRD patients with and without DM has not yet been performed. In this study, we assessed various structural and functional abnormalities in the CV system in ESRD patients and explored additive impact of DM on subclinical CV damage.

## MATERIALS AND METHODS

The current study used the Cardiovascular and Metabolic disease Etiology Research Center-High risk cohort (CMERC-HI) data, which is a prospective cohort study aimed at developing individual prevention strategies for patients with high risks of CV disease (clinicaltrials.gov NCT02003781). The CMERC-HI cohort enrolls patients who are 20 to 80 years old and meet at least one of the following inclusion criteria: high-risk hypertension patients [estimated glomerular filtration rate (eGFR) >60 mL/min with target organ damage or eGFR ≤60 mL/min]; DM patients with albuminuria; anuric ESRD patients on dialysis (urine output less than 200 mL/day); and relatives of acute myocardial infarction patients who were less than 55 years old for men or 65 years old for women. Exclusion criteria were a history of acute coronary syndrome, symptomatic coronary artery disease (CAD), symptomatic peripheral artery disease, heart failure, life expectancy less than 6 months due to non-CV disease, women who were pregnant or nursing, and a history of contrast allergy and related side effects. Finally, 1017 patients were enrolled between November 2013 and January 2015 at the Severance Hospital in Seoul, Republic of Korea. This study was performed in a subgroup of ESRD patients with anuria. The Institutional Review Board of the Yonsei University Health System Clinical Trial Center approved the study protocol, and the written informed consent was obtained from all participants.

Twenty-four hour ambulatory blood pressure monitoring (ABPM) was performed using a Takeda TM-2430 instrument (A&D Medical, Tokyo, Japan) with readings taken every 30 min. ABPM measurements were done on the arm without the arteriovenous fistula. Daytime and nighttime periods were defined according to information provided by the patient. Ambulatory blood pressure (BP) readings were averaged for 24 hours, daytime, and nighttime. Patients were classified according to dipping pattern as follows: dippers (nighttime BP decrease >10%), non-dippers (nighttime BP decrease <10% and >0%) and reverse dippers (nighttime BP > daytime BP).

Central hemodynamics were evaluated in the sitting position after 10 min of rest using the SphygmoCor system (AtCor Medical, Sydney, Australia). A high-fidelity micromanometer (Millar Instruments, Houston, TX, USA) was used to record peripheral pressure waveforms from the radial arteries as reported previously.<sup>4,5</sup> Radial artery waveforms were obtained from the arm without the arteriovenous fistula. The SphygmoCor system obtains the ascending aortic pressure waveform from the radial artery waveform using its validated mathematical transfer function. Central systolic BP, diastolic BP, pulse pressure, augmentation pressure, forward wave amplitude, and augmentation index (AI) were acquired from the aortic pressure waveform analyses. Pulse pressure was calculated as the difference between systolic and diastolic pressures. Augmentation pressure is the difference between the second and first

systolic peak pressures, and AI was defined as the ratio of augmentation pressure to aortic pulse pressure. The pulse wave velocity (PWV) was measured as specified previously.<sup>6</sup> Briefly, electrocardiogram and carotid/femoral pulse waves were obtained simultaneously to calculate the transit time using the foot-to-foot method. The distance traveled by the pulse wave was calculated by subtracting the sternal notch-right carotid site from right femoral site-sternal notch distances.<sup>6</sup>

In each patient, standard 2-dimensional transthoracic echocardiography was performed following The American Society of Echocardiography guidelines.<sup>7</sup> Left ventricular (LV) end-diastolic dimension (LVEDD) and LV end-systolic dimension (LVESD), end-diastolic interventricular septum (IVSd), and LV posterior wall thickness (PWd) were measured. LV mass was calculated using the formula  $0.8 [1.04 (IVSd + LVEDD + PWd)^3 - LVEDD^3] + 0.6$  (g) indexed to the body surface area. The LV ejection fraction (EF) was obtained using the modified Simpson's method. Left atrial (LA) volume was measured using the biplane area-length method indexed to the body surface area [left atrial volume index (LAVI)]. Using Doppler, peak velocities of early (E) and late diastolic mitral inflow were measured. Early (E') and late diastolic mitral annulus velocity were determined at the septal corner of the mitral annulus using tissue Doppler imaging. The ratio of E/E', which reflects LV filling pressure,<sup>8</sup> was calculated. Two experienced echocardiologists who were unaware of the patient's clinical information analyzed the echocardiographic data.

All testing, data acquisition, and image post-processing for coronary computed tomography angiogram (CCTA) were in accordance with the Society of Cardiovascular Computed Tomography guidelines on CCTA acquisition.<sup>9,10</sup> CCTA was performed with multi-detector row computed tomography scanners of 64 rows or greater (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan). Coronary arteries were evaluated according to a 16-segment coronary artery model modified from the American Heart Association classification.<sup>11</sup> Atherosclerotic plaques were defined as any structure >1 mm<sup>2</sup> within the vessel lumen or adjacent to the vessel lumen that could be clearly distinguished from the lumen and neighboring pericardial tissue or epicardial fat. CAD was defined as the presence of atherosclerotic plaques in each coronary artery segment. Minimal CAD was defined as coronary artery segments exhibiting plaques with <50% luminal narrowing, whereas significant CAD was defined as ≥50% luminal narrowing. The extent of significant CAD was categorized into 1-vessel disease (VD), 2-VD, and 3-VD. In addition, coronary artery calcium score (CACS) was measured in analyzable patients according to the scoring system described by Agatston, et al.<sup>12</sup> and Nakazato, et al.<sup>13</sup>

Continuous variables are expressed as mean±standard deviation after normality tests were performed for each parameter to assess whether a data set was normally distributed. Categorical variables were expressed as numbers and percentages. Variables of the two groups were compared using two-sample t-tests for continuous variables and chi-squared tests and Fish-

er's exact tests for categorical variables. In subgroup analyses for evaluating impact of dialysis modality, variables were compared by using the Mann-Whitney U test. Linear regression analyses and binary logistic regression analyses were performed to test the independent impact of DM on dependent variables.  $p < 0.05$  was considered statistically significant.

## RESULTS

The baseline clinical characteristics of patients are summarized in Table 1. Patients in the DM group had higher systolic BP, and therefore, they took more antihypertensive medications such as beta-blocker and calcium channel blocker than patients in

**Table 1.** Baseline Clinical Characteristics

Characteristics/Measures	DM (n=38)	Non-DM (n=53)	p value
Demography			
Age, yrs	56.0±13.0	51.2±13.6	0.096
Male, n (%)	22 (57.9)	30 (56.6)	1.000
Hypertension, n (%)	37 (97.4)	47 (88.7)	0.256
Mode of dialysis			0.894
Hemodialysis, (%)	23 (60.5)	34 (64.2)	
Peritoneal dialysis, (%)	15 (39.5)	19 (35.8)	
ESRD duration, yrs	16.0±25.6	13.4±13.7	0.575
Height, cm	163.4±8.9	162.4±9.3	0.590
Weight, kg	66.6±14.2	62.0±12.5	0.104
Body mass index, kg/m <sup>2</sup>	24.8±3.9	23.4±3.4	0.071
Waist, cm	87.4±11.9	83.2±9.5	0.065
Hip, cm	93.8±6.9	91.0±6.9	0.061
Thigh, cm	44.8±5.2	45.0±5.2	0.895
SBP, mm Hg	153.9±27.9	141.2±23.7	0.021
DBP, mm Hg	77.9±11.8	81.9±12.9	0.140
Heart rate, beats/min	70.8±11.8	70.8±14.0	0.994
Medications			
Insulin treatment, n (%)	12 (31.6)	0 (0)	<0.001
Beta-blocker, n (%)	26 (68.4)	24 (45.3)	0.048
ACEi/ARB, n (%)	26 (68.4)	31 (58.5)	0.456
CCB, n (%)	22 (57.9)	18 (34.0)	0.040
Statin, n (%)	19 (50.0)	16 (30.2)	0.090
Laboratory			
Hemoglobin, g/dL	10.2±1.7	10.9±1.4	0.033
Calcium, mg/dL	8.5±1.0	9.0±0.8	0.005
Phosphate, mg/dL	5.1±1.8	4.8±1.1	0.324
Glucose, mg/dL	128.3±58.3	94.3±19.4	0.001
BUN, mg/dL	52.5±23.1	59.6±23.5	0.158
Creatinine, mg/dL	9.7±3.5	10.5±3.7	0.294
Uric acid, mg/dL	6.3±1.9	6.4±1.7	0.956
Cholesterol, mg/dL	156.9±36.3	162.5±35.8	0.470
Triglycerides, mg/dL	126.4±86.5	105.6±43.2	0.184
HDL cholesterol, mg/dL	42.8±16.0	46.2±12.3	0.265
LDL cholesterol, mg/dL	85.7±28.6	87.2±27.1	0.804
Protein, g/dL	6.4±0.9	6.6±0.7	0.206
Albumin, g/dL	3.5±0.6	3.8±0.5	0.006
Sodium, mEq/L	137.8±3.3	138.5±2.8	0.265
Potassium, mEq/L	4.7±0.8	5.0±0.9	0.190
HbA1C, %	6.6±1.4	5.2±0.3	<0.001
C-reactive protein, mg/dL	7.3±14.7	4.3±7.7	0.267

ESRD, end-stage renal disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DM, diabetes mellitus; HbA1C, glycosylated hemoglobin.

the non-DM group. Other demographic findings were similar between the DM and non-DM groups. In laboratory findings, the DM group had higher fasting glucose and glycosylated hemoglobin levels. In addition, there were statistical differences

in hemoglobin, serum calcium, and albumin between the groups. However, uric acid levels and lipid profiles, which are well-known risk factors for CV diseases, did not differ between the two groups.

**Table 2.** Twenty-Four Hour-Ambulatory Blood Pressure Monitoring (ABPM) and Central Hemodynamics Assessed with Noninvasive Tonometry

	DM* (n=38)	Non-DM* (n=53)	p value
24-hr ABPM			
Dipper, n (%)	10 (27.0)	20 (38.5)	0.370
Non-dipper, n (%)	19 (51.4)	18 (34.6)	0.174
Reverse-dipper, n (%)	8 (21.6)	14 (26.9)	0.747
SBP, whole, mm Hg	149.8±23.1	142.4±23.7	0.147
DBP, whole, mm Hg	81.0±11.2	84.7±11.7	0.135
SBP, day, mm Hg	151.9±22.2	144.8±23.4	0.153
DBP, day, mm Hg	82.2±11.7	86.2±11.6	0.109
SBP, night, mm Hg	145.9±27.3	136.0±25.5	0.086
DBP, night, mm Hg	78.3±13.1	80.3±12.2	0.461
Central hemodynamics			
Central aortic systolic pressure, mm Hg	148.7±29.8	133.7±27.0	0.014
Central aortic diastolic pressure, mm Hg	82.6±13.8	83.9±13.4	0.663
Augmentation index@75	30.6±12.4	29.7±16.1	0.765
Pulse wave velocity, m/s	12.1±2.7	9.4±2.1	<0.001
Pulse wave velocity standard deviation, m/s	1.1±0.7	0.7±0.6	0.002

SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus.

\*One patient in the DM group and the non-DM group did not received ABPM.

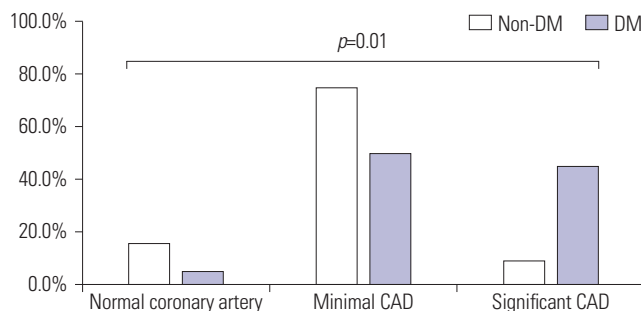
**Table 3.** Transthoracic Echocardiography and CCTA

Echocardiography	DM (n=38)	Non-DM (n=53)	p value
LVEDD, mm	52.1±5.2	51.8± 5.7	0.809
LVESD, mm	34.4±4.6	34.6± 5.1	0.910
LVEF, %	65.0±7.3	64.4± 8.3	0.738
IVSd, mm	11.3±1.8	10.9±1.8	0.256
PWd, mm	11.1±1.5	10.8±1.7	0.418
LVMI, g/m <sup>2</sup>	134.6±33.7	133.1±34.2	0.837
LAVI, mL/m <sup>2</sup>	65.1±21.0	58.6±21.5	0.159
E, cm/s	0.8±0.3	0.7±0.2	0.016
A, cm/s	1.0±0.2	0.8±0.2	0.001
E', cm/s	5.4±1.5	5.6±1.7	0.414
A', cm/s	8.6±1.7	8.3±1.9	0.593
E/E'	16.7±6.4	13.7±5.9	0.026
CCTA	DM (n=20)	Non-DM (n=32)	p value
Presence of CAD, n (%)	19 (95)	27 (84.4)	0.471
Presence of significant CAD, n (%)	9 (45)	3 (9.4)	0.009
Severity of CAD, n (%)			0.010
None	1 (5.0)	5 (15.6)	
Minimal CAD	10 (50.0)	24 (75)	
1-vessel	6 (30)	1 (3.1)	
2-vessel	2 (10)	1 (3.1)	
3-vessel	1 (5)	1 (3.1)	

LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; IVSd, diastolic interventricular septum; PWd, diastolic posterior wall thickness; E, early diastolic mitral inflow velocity; A, late diastolic mitral inflow velocity; LVMI, left ventricular mass index; LAVI, left atrial volume index; E', early diastolic mitral annulus velocity; A', late diastolic mitral annulus velocity; CCTA, coronary computed tomography angiography; CAD, coronary artery disease; DM, diabetes mellitus.

Data from 24-h ABPM, central hemodynamics, and PWV are shown in Table 2. Results from the 24-h ABPM were similar between the two groups. However, central aortic systolic pressure and PWV were significantly higher in DM patients compared to non-DM subjects ( $p<0.05$ ). Table 3 provides the data from echocardiography and CCTA examinations. In DM patients, E/E' was significantly higher despite similar LV EF, indicating that DM patients have higher LV filling pressure than non-DM patients.

CCTA was performed in 52 patients, and the presence of atherosclerotic plaques in each coronary artery segment was not different between the DM and non-DM groups (95% vs. 84.4%;  $p=0.471$ ) (Table 3). However, the prevalence of significant CAD was 23.1% ( $n=12$ ); and it was higher in the DM group (45%) than the non-DM group (9.4%). As shown in Fig. 1, it is noted that the prevalence of significant CAD (the presence of  $\geq 50\%$  stenosis in any major coronary artery) was greater in the DM group ( $p=0.010$ ). However, CACS, evaluated in analyzable pa-



**Fig. 1.** Coronary artery disease (CAD) severity according to the etiology of end-stage renal disease (ESRD). DM ESRD patients had more significant CAD compared to the non-DM ESRD group. DM, diabetes mellitus.

tients (20 non-DM patients and 19 DM patients), was not different between the groups (non-DM group,  $129.4\pm 263.8$ ; DM group,  $360.3\pm 678.7$ ;  $p=0.703$ ).

We performed statistical analyses to determine the association of clinical variables and the independent impact of DM on various vascular biomarkers. These data are provided in Table 4 and 5. The presence of DM independently determined central aortic pressure, PWV (Table 4), and the presence of CAD (Table 5) in both univariate and multivariate analyses. The presence of DM had significant association with E/E' in univariate analysis, however, it was not independent determinant for E/E' after adjustment with other variables (Table 4).

## DISCUSSION

The core findings of this study are: 1) despite similar demography, DM patients had higher central aortic systolic pressure and faster PWV; and 2) DM ESRD patients have more CAD and suffered from more severe CAD than non-DM ESRD patients. These results can be interpreted to indicate that DM ESRD patients have more advanced arteriosclerosis and more severe CAD than non-DM ESRD subjects. To the best of our knowledge, the current research is the first to assess the additive impact of DM on CV damage profile using a comprehensive screening protocol in ESRD patients who have a high risk of CV diseases. Based on the current data, we guardedly propose that more aggressive diagnostic work-ups and tailored management may be helpful for DM ESRD patients.

Although data from 24-h ABPM did not differ, DM ESRD

**Table 4.** Linear Regression Analyses for Independent Determinants of Central Systolic Aortic Pressure, Pulse Wave Velocity, and E/E'

Variable	Univariate model			Multivariate model		
	$\beta$	t	p value	$\beta$	t	p value
Central aortic systolic pressure						
Age	0.248	1.095	0.276	0.153	0.660	0.511
Male	2.032	0.329	0.743	3.379	0.561	0.576
ESRD duration	0.006	0.040	0.968	-0.001	-0.006	0.995
Peritoneal dialysis	-2.137	-0.339	0.736	-3.060	-0.474	0.637
DM etiology	14.986	2.503	0.014	15.950	2.593	0.011
Pulse wave velocity						
Age	0.082	4.115	<0.001	0.072	3.783	<0.001
Male	0.523	0.896	0.372	0.522	1.064	0.290
ESRD duration	0.003	0.195	0.845	-0.001	-0.047	0.963
Peritoneal dialysis	0.269	0.449	0.654	0.615	1.176	0.243
DM etiology	2.671	5.198	<0.001	2.262	4.511	<0.001
E/E'						
Age	0.143	3.009	0.003	0.120	2.392	0.019
Male	-2.393	-1.829	0.071	-2.287	-1.802	0.075
ESRD duration	-0.002	-0.076	0.940	0.008	0.239	0.812
Peritoneal dialysis	-1.360	-1.004	0.318	-0.558	-0.401	0.689
DM etiology	2.960	1.305	0.026	2.367	1.806	0.075

ESRD, end stage renal disease; DM, diabetes mellitus; E, early diastolic mitral inflow velocity; E', early diastolic mitral annulus velocity.



**Table 5.** Binary Logistic Regression Analyses for Determinants of Significant Coronary Artery Disease

Variable	Univariate model		Multivariate model	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.087 (1.016–1.187)	0.032	1.129 (1.015–1.312)	0.052
Male sex	10 (1.711–191.144)	0.035	1.734 (1.900–473.898)	0.031
ESRD duration	0.916 (0.803–0.999)	0.12	0.916 (0.742–1.014)	0.320
Peritoneal dialysis	1.115 (0.260–4.248)	0.876	1.493 (0.157–14.696)	0.721
DM etiology	7.5 (1.883–38.445)	0.007	6.651 (1.137–51.673)	0.046

ESRD, end stage renal disease; DM, diabetes mellitus; OR, odds ratio; CI, confidence interval.

patients had significantly higher central aortic systolic pressure, which is a robust prognosticator for CV outcomes and is superior to conventional brachial BP.<sup>14</sup> One potential explanation for this finding is more advanced arteriosclerosis in the DM ESRD group. This is further supported by our observation of faster PWV in these patients than non-DM ESRD subjects, despite similar clinical characteristics. In fact, the presence of DM, along with age, was an independent determinant for PWV in our cohort. Studies have shown that hyperglycemia and hyperinsulinemia accelerate arteriosclerosis through increased accumulation of advanced glycation end products and endothelial dysfunction.<sup>15,16</sup> In a study by Tomiyama, et al.,<sup>15</sup> increased BP and increased plasma glucose levels synergistically accelerated the progression of arterial stiffness in 2080 Japanese men. In the current investigation, we observed that the presence of DM independently correlated with more advanced arterial stiffness even in ESRD patients. This is clinically important because aortic stiffness is a strong independent predictor of CV mortality in subjects with end stage renal disease.<sup>17</sup>

In echocardiography examinations, however, the association between DM and E/E' showed marginal significance in multivariate analysis, and DM patients seemed to have higher E/E', which represents increased LV filling pressure.<sup>8</sup> This result suggests that: 1) DM ESRD patients might be prone to pulmonary congestion and/or heart failure symptoms during cardiac volume/pressure overload despite normal LV EF; and thus, 2) more aggressive LV unloading by renal replacement therapy and/or anti-heart failure medications should be considered in the setting of ESRD and DM.

Unexpectedly, E' and LA volumes did not differ between the DM and non-DM ESRD groups. E' reflects early diastolic LV longitudinal relaxation, which is more vulnerable and is an earlier manifestation of cardiac dysfunction than LV radial motion, which is commonly expressed by LV EF in various diseases affecting the heart.<sup>18</sup> It is well known that DM patients have blunted LV long-axis performances at rest<sup>19</sup> and during exercise.<sup>20</sup> As previously reported, diastolic dysfunction is more advanced in patients with DM<sup>19–21</sup> and ESRD;<sup>22</sup> however, our data failed to show any difference in LV relaxation properties between the two groups. In addition, LAVI, reflecting chronicity and severity of diastolic function, was not different between the two groups. Those results are plausibly explained by: 1) the longer duration of ESRD in the non-DM group, 2) characteristic chronic volume

overload status which overwhelms slight difference of myocardial dysfunction in ESRD patients, and 3) E' might be too rough to be used as a parameter to detect subtle differences in LV mechanics between the two groups. Thus, further studies are warranted using a more well-balanced and larger study sample and newer echocardiographic technologies, such as strain analysis, for better evaluation of myocardial function.

Although the overall prevalence of CAD (i.e., subclinical CAD) was modest (23.1%) in analyzable patients based on CCTA, the prevalence was apparently higher in the DM group (45%) than non-DM group (9.4%). Our data support the notion that DM may have a more negative impact on CV system even in ESRD patients, even though ESRD itself is a powerful risk factor for CV diseases and should be regarded as a 'CAD equivalent' condition. In DM ESRD patients, it is known that vascular calcification, chronic inflammation, and insulin resistance are kidney related CV risk factors.<sup>23</sup> However, the current study showed no difference of CACS and C-reactive protein levels between the groups. This observation suggests that different pathophysiologic mechanisms such as insulin resistance might have roles in generation and progression of CAD between ESRD patients with and without DM. ESRD has a strong relationship with the development of CV diseases, including atherosclerosis, due to the effects of uremia, volume/pressure overload of the heart and vessels, oxidative stress, and altered metabolism.<sup>24,25</sup> The clinical implication of our investigation is that when DM, which induces oxidative stress and inflammation,<sup>21</sup> is superimposed on ESRD, it affects the CV system in these patients.<sup>26</sup> Therefore, we carefully suggest a thorough diagnostic work-up for the detection and characterization of each patient's CV disease profile even in subclinical stages.

This study has some limitations. First, our small cohort limits the power of statistical analyses. Second, this is a single center study and included patients referred to a tertiary center. Thus, the current study group might not represent the entire population of patients with ESRD. Third, because of its cross-sectional design, we do not have CV outcome data in this cohort, and only observational data analyses were possible. In addition, baseline clinical characteristics were not matched between the DM and non-DM groups, although the differences were not statistically significant. Further investigations with larger ESRD population and long-term clinical outcome are needed to explore whether the comprehensive CV screening protocol could

help prevent future CV event in DM ESRD patients.

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## REFERENCES

- Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-305.
- Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 1998;339:799-805.
- Ritz E, Rychlík I, Locatelli F, Halimi S. End-stage renal failure in type 2 diabetes: a medical catastrophe of worldwide dimensions. *Am J Kidney Dis* 1999;34:795-808.
- Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Berent R, et al. Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation* 2004;109:184-9.
- Weber T, O'Rourke MF, Ammer M, Kvas E, Punzengruber C, Eber B. Arterial stiffness and arterial wave reflections are associated with systolic and diastolic function in patients with normal ejection fraction. *Am J Hypertens* 2008;21:1194-202.
- Rajzer MW, Wojciechowska W, Kloczek M, Palka I, Brzozowska-Kiszka M, Kawecka-Jaszcz K. Comparison of aortic pulse wave velocity measured by three techniques: Complior, SphygmoCor and Arteriograph. *J Hypertens* 2008;26:2001-7.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-63.
- Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22:107-33.
- Hendel RC, Patel MR, Kramer CM, Poon M, Hendel RC, Carr JC, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 2006;48:1475-97.
- American College of Cardiology Foundation Task Force on Expert Consensus Documents, Mark DB, Berman DS, Budoff MJ, Carr JJ, Gerber TC, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation* 2010;121:2509-43.
- Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975;51(4 Suppl):5-40.
- Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827-32.
- Nakazato R, Dey D, Gutstein A, Le Meunier L, Cheng VY, Pimentel R, et al. Coronary artery calcium scoring using a reduced tube voltage and radiation dose protocol with dual-source computed tomography. *J Cardiovasc Comput Tomogr* 2009;3:394-400.
- Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006;113:1213-25.
- Tomiyaama H, Hashimoto H, Hirayama Y, Yambe M, Yamada J, Koji Y, et al. Synergistic acceleration of arterial stiffening in the presence of raised blood pressure and raised plasma glucose. *Hypertension* 2006;47:180-8.
- Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005;25:932-43.
- Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999;99:2434-9.
- Urbano-Moral JA, Rowin EJ, Maron MS, Crean A, Pandian NG. Investigation of global and regional myocardial mechanics with 3-dimensional speckle tracking echocardiography and relations to hypertrophy and fibrosis in hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging* 2014;7:11-9.
- Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. *Diabetes Care* 2001;24:5-10.
- Kim SA, Shim CY, Kim JM, Lee HJ, Choi DH, Choi EY, et al. Impact of left ventricular longitudinal diastolic functional reserve on clinical outcome in patients with type 2 diabetes mellitus. *Heart* 2011;97:1233-8.
- Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. *Endocr Rev* 2004;25:543-67.
- Hayashi SY, Brodin LA, Alvestrand A, Lind B, Stenvinkel P, Mazza do Nascimento M, et al. Improvement of cardiac function after haemodialysis. Quantitative evaluation by colour tissue velocity imaging. *Nephrol Dial Transplant* 2004;19:1497-506.
- Wang AY. Cardiovascular risk in diabetic end-stage renal disease patients. *J Diabetes* 2011;3:119-31.
- Meeus F, Kourilsky O, Guerin AP, Gaudry C, Marchais SJ, London GM. Pathophysiology of cardiovascular disease in hemodialysis patients. *Kidney Int Suppl* 2000;76:S140-7.
- Zoungas S, Ristevski S, Lightfoot P, Liang YL, Branley P, Shiel LM, et al. Carotid artery intima-medial thickness is increased in chronic renal failure. *Clin Exp Pharmacol Physiol* 2000;27:639-41.
- Ishii H, Toriyama T, Aoyama T, Takahashi H, Amano T, Hayashi M, et al. Prognostic values of C-reactive protein levels on clinical outcome after implantation of sirolimus-eluting stents in patients on hemodialysis. *Circ Cardiovasc Interv* 2009;2:513-8.